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EXAMINER
ZISKA,S

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1804

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MORRISON & FOERSTER
2000 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20006-1812

1804

DATE MAILED:
09/14/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/1/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This application should be reviewed for errors.

This Office Action is in response to the amendment filed After Final on August 1, 1995, requesting removal of Finality. Applicant's arguments have been found to be persuasive and the Finality is withdrawn. The amendment has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12 are active and examined in this Office Action.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-39, 68, 69 and 82 of copending application serial no. 08/031,801 is maintained. Applicants have stated that they prefer to defer submission of any terminal disclaimers pending notification of allowable subject matter. In view of Applicant's arguments, the rejection is maintained.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 30 and 33-35 of copending application serial no. 07/919,297 is maintained. Applicants have stated that they prefer to defer submission of any terminal disclaimers pending notification of allowable subject matter. In view of Applicant's arguments, the rejection is maintained.

The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, remains as follows: the rejection directed to the ES cell line is withdrawn in view of the amendments to the claims. Further, the objection to the claims regarding the term "rodents" and "murine" is withdrawn. The rejection of claims 5-11 requiring the limitation to the J region or kappa constant regions or J and kappa constant region is withdrawn.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, regarding the phrases "substantially intact" and "and/or" is withdrawn in view of the amendments to the claims.

The rejection of claims 1-6, 8 and 9 under 35 U.S.C. 103 as being unpatentable over Huxley taken with Hooper and Pachnis is maintained.

The rejection of claims 7, 10 and 11 under 35 U.S.C. 103 as being unpatentable over Hooper taken with Huxley and Pachnis is maintained.

Applicant's arguments, filed August 1, 1995, have been considered but not found to be persuasive. Applicants have argued the rejections simultaneously and therefore their arguments are similarly rebutted. Applicants have argued that the cited references considered as a whole and when taken with those articles submitted for the record by applicants, do not suggest the claimed invention. Applicants have argued that the Examiner has inferred a reasonable expectation of success from the statement of Pachnis (page 5113, left column, last paragraph) and that such a statement was an unwarranted conclusion on the part of the examiner. However, Pachnis did make the statement and it is the examiner's position that Pachnis provides a reasonable expectation of success.

Applicants have argued that the reference does not say that L and ES cells are equivalent and it provides no extra guidance for transforming ES cells. However, the claims are not drawn to methods for transforming ES cells; Pachnis apparently believes the methodology as applied to L cells would be applicable to ES cells and Pachnis was cited in combination with Hooper, teaching ES cells and Huxley, teaching transfer of human genes on YACS to mouse L cells by cell fusion. Pachnis provides no teaching away from the substitution or provides reasons as to why the substitution would not be expected to work. Applicant's arguments regarding the lack of a reasonable expectation of success are not persuasive. Applicants have argued the methods as applied to L cells would fail when applied to ES cells but have failed to

support their assertions with evidence. Merely because Strauss found that lipid micelles are "inefficient and irreproducible" does not mean that ES cells cannot be transformed with other methods applied to L cells and successfully used.

Applicants have argued that the record as exemplified by Strauss (1993) contains evidence that techniques useful in transfecting fibroblasts would not have been expected to work in ES cells as has now been disclosed and claimed by applicant; that Strauss 1993 was submitted and reported no successful transfection of ES cells had been reported to date and that therefore the Pachnis techniques were not readily applied to ES cells. However, Pachnis does infer a reasonable expectation of success otherwise he would not have suggested the substitution. Applicants have argued that in two of the references, both by Strauss, the authors of the papers used a technique involving lipofection with purified YACs in order to avoid problems associated with spheroplast fusion and Applicants cite Strauss at page 421, right hand column, for support. However, the cited paragraph does not contain a single teaching that there is a problem in the use of spheroplasts per se. Applicant's cited paragraph does not support their arguments. Strauss (Science) used micelles, not spheroplasts, and with a subsequent modification of their initial protocol was able to achieve integration and expression of YACs. There is no mention of the use of spheroplasts or comparison of their method with the spheroplast method. Strauss (EMBO) discloses that the YACs constitute such a small fraction of the DNA available for transfection and "not surprisingly" several investigators found large portions of the yeast genome present in their stable transfectants. Apparently, the reason that investigators using the spheroplast technique have not been able to achieve transfection of ES cells is that a large amount of the DNA in the

spheroplast is the yeast genome and not the YAC of interest. Therefore, the inability to achieve transfection is not related to the spheroplast technique per se but to the relative ratios of "junk" DNA compared to the desired DNA. Such reasoning is supported by both of the Strauss articles, which showed integration into the ES genome when using purified YACs contained in micelles. There is no evidence in these references that spheroplast fusion would not work. If it is true that most ES cells contained junk DNA (yeast DNA, not the YAC DNA which would contain the gene of interest)after spheroplast fusion, then integration into the ES cell genome is seen to be a reflection of the concentration of YAC DNA and since spheroplasts contain mostly junk DNA, the number of transfectants screened would have to be larger than the number screened if there were less junk DNA. Since identification of the clone containing the YAC DNA is relatively straight forward using techniques already available in the prior art as well as the submitted art, the references do not teach away from using the spheroplast technique. Strauss and Strauss are useful for pointing out that once the YAC is purified away from the junk DNA, which is to say that once the concentration of desired YAC DNA is increased compared to the concentration of the yeast DNA, ES cells are readily transformed. Thus in the spheroplast method, at least one ES cell would contain the YAC DNA and would not be subject to the postulated "mutagenic influences" only postulated to exist by Strauss and relied upon by applicants as evidence of lack of reasonable expectation of success.

Applicants have argued that taken for what they fairly disclose to one skilled in the art, the two Strauss papers report that the specific Pachnis fibroblast fusion technique was problematic. However, contrary to such arguments, Strauss

(Science) used lipid micelles and lipid micelles are not identical to yeast spheroplasts.

Applicants have argued that the record does not support the conclusion of the examiner who considers that Strauss does not teach away from using the spheroplast fusion and that the problems in utilizing the protocols of Pachnis would have been overcome simply by preparing and screening more clones because Strauss was concerned by mutagenesis and not simply the logistics of screening more cells. However, contrary to such arguments, even if insertion of yeast DNA resulted in mutagenesis, simple screening of ES cells would identify those cells having the desired insertion.

Applicants have argued that (page 9, this amendment)

"Thus, the evidence of record explains that *Strauss et al.* utilized lipid micelles as an alternative technique to spheroplast fusion, thereby teaching away from the *Pachnis et al.* procedures, not because of an inability to screen larger numbers of clones, but rather to avoid the mutagenic impact of the presence of a large amount of yeast DNA".

However, contrary to such arguments, Strauss never discloses that lipid micelles are used as an alternative technique to spheroplast fusion because spheroplast fusion does not work. Strauss (Science)discloses that the use of lipid micelles was improved by using a "cleaner" DNA, exposing the cells to the DNA-lipid complex in suspensions instead of growing as a monolayer, isolating the DNA in spermine and adding poly-L-lysine prior to the addition of the cationic lipid DOTAP (page 1905, column 1, second full paragraph). Lacking evidence to the contrary, simply screening larger numbers of clones would overcome the large number of clones found to contain mutagenic material, if any clones were found to be "mutagenic". Furthermore, Strauss addresses "injected DNA", not spheroplast-introduced DNA. Strauss discloses that "Because DNA injected into mammalian embryos is

highly mutagenic, it is possible that the presence of yeast DNA in the transfected ES cells interferes with their ability to contribute to the germ line". Strauss therefore specifically addresses injected DNA, not DNA inserted by spheroplast fusion, and applicant's arguments regarding the mutagenicity of yeast DNA are not persuasive. Further, Strauss (EMBO, page 421, second column, last paragraph) clearly states that "This material **could** be mutagenic..." (emphasis added) and not that it was. Note that if yeast DNA were truly mutagenic in ES cells, then insertion of any yeast DNA by any method would result in high rates of mutagenicity, lacking evidence to the contrary and applicants' cited art simply does not teach this. Therefore, neither of *Strauss et al.* teach away from using spheroplast fusion to transfer yeast DNA to ES cells and the issue of whether the DNA per se is mutagenic remains unresolved.

Applicants have argued that regarding Pavan, one skilled in the art would learn from Pavan that ES cells are fragile and loose the ability to colonize germ lines and that this would not increase whatever expectations of success remained after a consideration of the other evidence of record previously discussed. However, as previously stated in the prior Office Action, ES cells are known in the art to lose the ability to colonize the germ line no matter what transfection technique is applied. Further, this characteristic of ES cells was old and well known to those ordinary skill in the art long prior to the publication of Pavan. See Bradley, of record, page 535, column 1, for confirmation of the examiner's statement.

Applicants have argued that the fourth reference, Bradley, teaches that it was only "potentially" that YAC vectors could be transferred to ES cells and that the state of the art in 1992 presented no reasonable expectation of success. However, contrary to such arguments, Bradley does not provide evidence as to why

YACs would not be expected to work and "potentially" is not the equivalent of "would not be expected". Further, Pachnis clearly postulated the successful use of the YAC transfer system to ES cells as argued above.

The rejection of claim 12 under 35 U.S.C. § 103 as being unpatentable over Huxley, Hooper and Pachnis as applied to claims 1-6, 8 and 9 above, and further in view of Traver et al., Shimizu et al. and Berman et al is maintained. Applicants have argued that the additional references Traver, Shimizu and Berman does not fill the gaps left by the primary and secondary references and that not withstanding knowledge of transgenes containing rearranged human immunoglobulin related gene, one skilled in the art still would have had no reasonable expectation of success in the methods disclosed in claim 12 as set forth by applicants. However, the sufficiency of the teachings regarding the reasonable expectation of success as taught the primary and secondary references have been discussed above and is repeated herein.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800